REMARKS

Applicants thank the Examiner and the Supervisory Examiner for the courtesies extended at the interview with Applicants' representatives on October 8, 2003.

Entry of this amendment is respectfully requested, as it is believed to be fully responsive to the Examiner's rejections and to the concerns expressed at the interview; would not require new search; and would place the application in condition for allowance.

Reconsideration and allowance are respectfully requested.

Claims 35, 36, 39, 40, and 43-53 were pending. In this amendment, claims 39, 44, and 48 are cancelled; claims 35 and 40 are amended to incorporate the limitations of claims 44 and 48; claim 40 is amended to place it in independent form; claim 49 is amended to delete a reference to estradiol derivatives; and claims 49-51 are amended to change their dependency. No new matter is added. Accordingly, claims 35, 36, 40, 43, 45-47, and 49-53 are pending and at issue.

Rejections Under 35 U.S.C. § 112

Claim 49 has been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement, and under 35 U.S.C. § 112, second paragraph, for indefiniteness, for the recitation of estradiol derivatives other than estradiol. This rejection is respectfully traversed.

As discussed in the Amendment filed April 20, 2003, Applicants believe that (i) one of ordinary skill in the art would recognize that therapeutically equivalent estrogens could be used in practicing the present invention in place of estradiol without undue experimentation and (ii) therapeutically equivalent estradiol derivatives are known and understood in the art and therefore do not render the claim indefinite. Nonetheless, to expedite prosecution, claim 49 has been amended to encompass estradiol. It is respectfully submitted on this basis that these rejections has been overcome.

Rejection Under 35 U.S.C. § 103

Claims 35, 36, 39, 40, and 43-53 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Mettler et al., in view of Meignant (WO 97/12600), Vagifem® monograph (Novo Nordisk® 2000), and Smith et al., *Maturitas* 16:145, 1992. The Examiner contends that Mettler et al. discloses the use of estradiol to treat atrophic vaginitis; that

Meignant discloses that dosage forms having less than 10 μg estradiol are useful for reducing systemic absorption; that the Vagifem® monograph discloses tablets containing hypromellose and PEG in their coating; that Smith et al. discloses that 5-10 μg of estradiol is effective to treat atrophic vaginitis, and that it would have been obvious to combine the teachings of these citations to achieve the presently-claimed invention. This rejection is respectfully traversed.

The Examiner has brought a new ground of rejection, which is apparently based on the Smith et al. article. While Applicants do not dispute that Smith et al. "clearly teaches the employment of 5-10 μg of estradiol in the treatment of atrophic vaginitis" (Office Action at page 7), it is pointed out that the study described in Smith et al. involved administering 5-10 μg of estradiol *daily* (see, e.g., abstract and page 147, third paragraph, both of which clearly state that the vaginal ring that was employed in the study released 5-10 μg of estradiol *per 24 h*, i.e., 35-70 μg/week.)

Accordingly, Smith et al. is remote from the present invention, which is based on the finding that distinctly lower doses of estradiol, e.g., up to about 20 μg/week, is effective in treating symptoms associated with estrogen deficiency.

With respect to Meignant, the Examiner's attention is directed to US Patent No. 6,060,077 (the "'077 patent"), which is an English version of WO 97/12600 cited by the Examiner. Meignant relates to an allegedly improved formulation for local vaginal administration of estradiol. As will be discussed in detail below, Meignant is remote from the present invention with respect to both the type of formulation and the dosing regimen required by the present claims.

First, Meignant relates to a galenical formulation comprising estradiol in solution or suspension combined with a lipophilic agent, a hydrophilic gel-forming bioadhesive agent, and a hydrodispersable agent (such as, e.g., in a soft capsule.) The formulation of Meignant is quite different from a tablet formulation as utilized in the presently claimed invention.

Second, Meignant does not disclose or suggest a low-dose treatment *regimen* as in the present invention. See,

> The dosage must be selected so as to relieve local problems and prevent transvaginal absorption to a maximum extent.
>
> These aims are achieved by selecting a dose of 10 μg of 17-b-estradiol, corresponding to a unit dose (a single daily administration, or less frequently still). *('077 patent, column 4, lines 20-25)*

In other words, to the extent that Meignant provides any guidance relating to a treatment regimen, it is a regimen corresponding to 70 μg estradiol per week, which is far above the dosages encompassed by the present claims. Even given the "less frequently still" suggestion, it would require a *much* less frequent dosing regimen (i.e., $1/3^{rd}$ -$1/7^{th}$ the dosing regimen explicitly suggested by Meignant) to even approach the range of the present invention, and there is no hint or suggestion in Meignant of this level of reduction of the dosing regimen.

Furthermore, the only information offered by Meignant with respect to a dosing regimen is in relation to a unit dosage form containing 10 μg estradiol. With respect to unit dosage forms containing 2.5 μg, 5 μg, or 15 μg estradiol, Meignant offers no dosing information at all. Meignant specifically does *not* state that these are *daily* doses, which is particularly significant in view of the observation that the plasma level of estradiol peaks at 1 hour after administration of the dosage forms of Meignant (see, '077 patent, column 4, lines 26-30, immediately adjacent). Consequently, one of ordinary skill in the art, taking all of the disclosure of Meignant in context, would reasonably infer that Meignant is suggesting that dosages less than 10 μg may be used, *if* they are administered more frequently (i.e., more than once daily), with the aim of not increasing the plasma concentration of estradiol.

That Meignant did not contemplate that administration of 10 μg of estradiol as infrequently as once or twice weekly could be an effective regimen is supported by the single clinical study disclosed in Meignant. (see, column 6, line 38 – column 7, line 23). Subjects were administered a *single* dose of estradiol, after which plasma estradiol levels were measured. No evidence is presented that addresses clinical efficacy in treating atrophic vaginitis, raising the inference that multiple dosing (at an unknown frequency) would be required to achieve clinical effects.

Meignant also teaches away specifically from the present invention. See, '077 patent at column 1, lines 53-58, which states (discussing the use of tablets for vaginal administration of estradiol): "However, because of their particular galenical form, the dosage of such tablets must be relatively high to obtain the desired results, typically a dosage of 25 micrograms (μg) of 17-b-estradiol per tablet (one tablet corresponds to one unit dose) to provide the desired cytological, histological, and clinical improvement in the vaginal mucous membrane."

In summary, in view of the stated goal of Meignant (to reduce the systemic absorption of estradiol by changing the formulation from a tablet to one in which the estradiol

is in solution or suspension), one of ordinary skill in the art, reading Meignant, would not be motivated to attempt once or twice-weekly administration of a tablet having, e.g., 10 μg as in the present invention. Furthermore, in the absence of any clinical data at all (much less, any clinical data directly relevant to the presently claimed treatment regimen), Meignant could not have provided one of ordinary skill with any expectation of success at achieving the benefits of the present invention.

Mettler et al. teaches away specifically from the present invention. Mettler et al. relates to Applicants' current product, Vagifem®, which is a tablet containing 25 μg estradiol that is administered twice weekly. Mettler et al. compares twice-weekly administration of 25 μg estradiol with once-weekly administration of 25 μg estradiol and concludes ":...twice-weekly administration of 25 μg E2 is the lowest effective dose for the long-term treatment of post-menopausal oestrogen-deficiency-derived atrophic vaginitis" (Mettler et al., page 30, second full paragraph). Mettler et al. also states, "Twice-weekly administration of 25 μg E2 seems to be the lowest effective dose for the successful treatment of such symptoms" (Mettler et al, page 30, 5th full paragraph). It is further pointed out that the currently claimed regimens (10 μg once or twice a week or 5 μg twice a week) are below even the once-weekly 25 μg administration deemed unsatisfactory by Mettler et al., thus lowering still further any expectation of success that could be afforded by Mettler et al.

In summary, prior to the present invention, it was generally accepted by those of ordinary skill in the art of hormone replacement therapy that effective treatment of atrophic vaginitis using local, vaginal, administration of estradiol required at least 35-50 μg/week (and, in some cases, 70 μg/week) of estradiol. None of the cited references, either singly or in combination, nor any other citations of which Applicants are aware[1], could have provided either the motivation to attempt a lower dosage regimen or the reasonable expectation of success in achieving the benefits of the present invention.

By contrast, as discussed at the interview and as illustrated in the Examples of the present specification, the present inventors have provided experimental evidence that vaginal administration of lower doses of estradiol tablets results a therapeutic effect comparable to that achieved with higher doses, without the systemic absorption of estradiol (and attendant higher risk of side effects) associated with the higher doses. Specifically,

[1] The Examiner's attention is directed to the following three citations, which are being filed concurrently herewith in an Information Disclosure Statement: Kvorning, in "The Urogenital Oestrogen Deficiency Symdrome", Saldioe and Eriksen, eds., 1986, pages 51-61; Nilsson et all, *Maturitas* 15:121-127, 1992; and Dugal et al., *Acta Obstet Cynecol Scand* 79:2930297, 2000.

using the presently claimed methods, the patients' average serum estradiol concentrations were consistently within the normal postmenopausal range, while at the same time the patients experienced significant improvement in vaginal morphology (maturation value) relative to baseline values. It is believed that the present invention provides an unexpected benefit of a magnitude that supports patentability of the present claims.

On this basis, it is respectfully submitted that the presently claimed invention is non-obvious over the cited references and that this rejection should be withdrawn.

It is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

Date: October 16, 2003

Reza Green, Reg. No. 38,475
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800